Neurobiological and Clinical Consequences of Stress

From Normal Adaptation to Post-Traumatic Stress Disorder

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26

Towards Pharmacotherapy for Post-Traumatic Stress Disorder

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PATHOPHYSIOLOGY OF PTSD: IMPLICATIONS FOR PHARMACOTHERAPY

Post-traumatic stress disorder (PTSD) appears to be a very complicated disorder. As many previous chapters suggest, a number of neurobiological systems are affected by exposure to catastrophic stress. There is a large body of experimental data on animal models for PTSD, including inescapable stress, conditioned fear, fear-potentiated startle, kindling, behavioral sensitization, and time-dependent sensitization. Taken together they suggest that at least seven or eight neurobiological systems that mediate cognitive, emotional, and behavioral processes involved in coping, adaptation, and survival may be dysregulated in PTSD. This impression is bolstered by human stress and PTSD research, also reviewed in previous chapters, although the data are not as comprehensive as in the animal studies. At this point in time it appears that PTSD is probably associated with abnormalities in the adrenergic, hypothalamic-pituitary-adrenocortical (HPA), opioid, dopaminergic, and thyroid systems, and possibly with alterations in the serotonergic, gamma-aminobutyric acid (GABA)-benzodiazepine and the *N*-methyl-D-aspartate (NMDA) systems. As yet, we have no evidence that neural input from these various systems is funneled through some final common pathway that may be definitively modified by pharmacological intervention.

It is important to keep this in mind as we review the current literature on the clinical psychopharmacology of PTSD. To present one of our conclusions in advance, given the complex pathophysiology of this disorder, effective pharmacotherapy for PTSD may require a multisystem approach in which several drugs, each with a unique and distinct action, are administered simultaneously.

CLINICAL PSYCHOPHARMACOLOGY—OVERVIEW

In their comprehensive review of the treatment outcome literature on PTSD, Solomon and associates (1) noted that a total of 255 English language reports on treatment of PTSD had been published, of which only 11 studies were randomized clinical trials (RCTs), 5 pharmacological, and 6 behavioral. The five drug studies in-

cluded three trials of tricyclic antidepressants (TCAs) and two trials of monoamine oxidase inhibitors (MAOIs). Three other controlled trials should be mentioned: an A-B-A test of propranolol (2), an RCT of alprazolam (3), and a recently reported RCT with fluoxetine (4).

Given the paucity of RCTs and our belief that data from open trials and case reports should not be ignored, we will present a comprehensive review of the entire literature on clinical pharmacology of PTSD in this chapter. Although we give much greater weight to RCTs, we will discuss a recently published quantitative analysis that synthesizes RCT and non-RCT results regarding TCAs and MAOIs (5). We do so with the full understanding that, without an RCT, there are always serious questions about sampling, subject selection, and interpretation of results. Furthermore, there is an editorial bias such that positive rather than negative findings are much more likely to be published in an open trial or case report, whereas that is not true for randomized clinical trials.

CLINICAL PSYCHOPHARMACOLOGY—REVIEW OF THE LITERATURE

In this section we will review published data on drug trials in PTSD. Rather than present a tabulation of results with drug X or drug Y, we will offer a conceptually driven review that begins with more specific pharmacological agents and works towards more complex drugs such as TCAs or MAOIs. Therefore, we will review: 1) drugs affecting the adrenergic system (clonidine and propranolol); 2) drugs affecting the serotoninergic system (fluoxetine, buspirone, fluvoxamine, clomipramine, and cyproheptadine); 3) drugs affecting both systems (TCAs and MAOIs); 4) drugs affecting the GABA-benzodiazepine system (alprazolam and clonazepam); 5) anticonvulsants with antikindling properties (carbamazepine and valproate); 6) lithium and drugs affecting the dopamine system (neuroleptics); and 7) drugs affecting endogenous opioid activity (narcotic antagonists). A general summary of this review is shown in Table 1.

Drugs Affecting the Adrenergic System—Propranolol and Clonidine

PTSD has repeatedly been shown to be associated with excessive adrenergic activity. As reported earlier (see Chapters 18 and 19), patients with PTSD exhibit increased 24-hour urinary catecholamine levels, downregulation of alpha-2 and beta adrenergic receptors, and excessive responsitivity to the alpha-2 antagonist, yohimbine. For these reasons, one would predict that sympatholytic agents such as propranolol and clonidine would have an important place in the treatment of PTSD. Clonidine is an alpha-2 adrenergic agonist and propranolol is a postsynaptic beta adrenergic blocking agent. Both drugs reduce sympathetic arousal and adrenergic activity through different mechanisms of action. Furthermore, both drugs have demonstrated efficacy in the treatment of anxiety (6–8).

Surprisingly, there has been very little interest in either drug, despite the fact that Kolb et al. (9) reported promising results with both clonidine and propranolol as early as 1984. In open trials with nine Vietnam veteran PTSD patients, both drugs reduced traumatic nightmares, intrusive recollections, hypervigilence, insomnia, startle reactions, and angry outbursts. Perry et al. (10), in an open trial using clonidine for the treatment of 17 children with PTSD (0.05–0.1 mg twice a day), noted a profound improvement in behavioral impulsivity, anxiety, arousal, concentration, and mood. Kinzie and Leung (11) had favorable results with clonidine in combination with the TCA imipramine in Cambodian refugees who met diagnostic criteria for both PTSD and depression; in addition to improvement in depression, PTSD symptoms such as nightmares, insomnia, and startle reactions responded favorably to this treatment. There are other reports as well, suggesting that Southeast Asian refugees with PTSD can be treated successfully with the clonidine/imipramine combination (12).

There are three reports on propranolol use in PTSD patients. It successfully reduced intrusion and arousal symptoms in Vietnam veterans, as just noted (9), was ineffective in an open trial with Cambodian refugees (13), and was used successfully in American children whose PTSD

TABLE 1

Drug category	Drug	Daily dose	Hypothesized mechanism of action	# RCT	Remarks
Adrenergic Inhibitors	Clonidine	0.2–0.4 mg	Alpha 2 Agonist	0	Promising results in studies on B & D symptoms.
	Propranolol	130–160 mg	Beta Blocker	0	2 positive, 1 negative study. Successful trial with children on B & D symptoms.
Drugs Affecting Serotonergic Mechanisms	Fluoxetine	20–80 mg	SSRI	1	Only drugs consistently effective on C symptoms.
	Fluvoxamine	250–300 mg	Antidepressants	0	Effects on B & D symptoms less conclusive.
	Clomipramine	200–150 mg	TCA with SSRI Actions	0	One open trial, too little data. Reduced B symptons only.
	Buspirone	35–60 mg	5HT1A Partial Agonist	0	Case reports on 3 patients. Too little data. Only reduced B & D symptoms.
	Cyproheptidine	4–28 mg	5-HT Antagonist	0	Case reports only. Seems effective primarily on traumatic nightmares.
TCA Antidepressants	Imipramine	150–300 mg	NE/5-HT Reuptake Inhibitors	1	Quantitative analysis of RCTs and open trials suggests primary effect on B symptoms and global PTSD severity—not on C or D symptoms.
	Amitriptyline			1	
	Desipramine			1	
MAOI Antidepressants	Phenelzine	45–75 mg	Inhibits metabolism of NE and 5-HT	2	More effective than TCAs but quantitatively shows same spectrum of action.
Benzodiazepine Anxiolytic	Alprazolam	0.5–6 mg	Benzodiazepine Agonist	1	Reduce general anxiety symptoms but no conclusive actions on core PTSD symptoms. Only 3 studies.
	Clonazepam	1–6 mg		0	
Anticonvulsant	Carbamazepine	600–1000 mg	Antikindling Action	0	5 open studies. Effective on B & D symptoms.
	Valproate	750–1750 mg		0	3 open studies. Effective on C & D symptoms.
Antimanic Agent	Lithium	300–1500 mg	Multiple Actions	0	2 open trials. Appears to reduce D symptoms only.
Antipsychotic Agent	Thioridazine	200 mg	DA Antagonist	0	Not firstline drugs. 1 case report: effective on B & D symptoms.
Narcotic Antagonists	Nalmefene	200–400 mg	Opioid Antagonists	0	Open trial-mixed results: reduced C as well as B & D symptoms in some patients, but made others worse.
	Naltrexone	50 mg		0	1 case report: reduced flashbacks in two patients.

Abbreviations: PTSD B symptoms: intrusive recollections, traumatic nightmares, flashbacks, etc.
PTSD C symptoms: avoidant behavior, psychic numbing, dissociation, etc.
PTSD D symptoms: insomnia, irritability, startle, hypervigilance, hyperarousal, etc.
DA, dopamine; 5-HT, serotonin; MAOI, monoamine oxidase inhibitor; NE, norepinephrine; RCT, randomized clinical trial; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

was precipitated by physical and/or sexual abuse (2). This latter study, though not a RCT, was an A-B-A design (6 weeks off—6 weeks on—6 weeks off medication) in which subjects received 2.5 mg/kg/day. Significant reductions in intrusion and arousal symptoms were observed in 8 of 11 children. In some cases, propranolol was discontinued if the pulse rate fell below 50 beats per minute or the diastolic blood pressure fell below 50 mm Hg.

Drugs Affecting the Serotonergic System—Fluoxetine, Fluvoxamine, Clomipramine, Buspirone, and Cyproheptadine

A number of the growing family of serotonin receptors (specifically the 5-HT_{1a}, 5-HT_2, and 5-HT_3) appear to mediate anxiety reactions (14). Furthermore, the pathophysiology of obsessive-compulsive disorder (OCD) clearly involves serotonergic mechanisms. This is of particular interest since the obstinate persistence of PTSD intrusive recollections sometimes resembles the pattern of obsessional thoughts in OCD, while the repetitive predictability of some avoidant behaviors is reminiscent of compulsive patterns in OCD. In addition, certain symptoms or syndromes frequently associated with PTSD (impulsivity, aggressiveness, suicidal intent, alcoholism, substance abuse, depression, and personality disorders) bring the serotonergic system to mind (15).

Despite the intriguing inferences just cited, only two preliminary studies have investigated serotonergic mechanisms in traumatized patients. Southwick et al. (16) administered the serotonergic agonist MCPP (m-chlorophenylpiperazine) to 14 Vietnam veterans with PTSD. Thirty-six percent experienced panic attacks and 25% exhibited trauma-related dissociative episodes and flashbacks, in contrast to non-PTSD combat controls who did not respond to MCPP. Corrigan et al. (17) reported significant blunting of both the prolactin and cortisol responses to intravenous clomipramine in adult female survivors of childhood sexual abuse in comparison with a nontraumatized control group. Such findings suggest that serotonergic abnormalities may be present in PTSD patients. With this in mind, we shall review published results on selective serotonin reuptake inhibitors (SSRIs), clomipramine (a TCA with SSRI-type action), buspirone (an anxiolytic 5-HT_{1A} partial agonist), and cyproheptadine (a 5-HT receptor antagonist).

SSRIs and Associated Drugs—Fluoxetine, Fluvoxamine, and Clomipramine

There are currently 5 published open trials and case reports with the SSRI fluoxetine, involving a total of 71 patients with PTSD, all but 5 of whom were American war-zone (mostly Vietnam) veterans. The remaining five were nonveteran men and women exposed to civilian trauma. Two studies were carried out at the National Center for PTSD, where marked improvement in intrusive, avoidant, and arousal symptoms was observed in 13 of 20 Vietnam veterans (18), and where marked or moderate improvement was observed in 12 of 19 military veterans (19). An interesting report by March (20) described moderate remission of PTSD symptoms in a Vietnam veteran receiving fluoxetine and later fluvoxamine who had failed to respond to other drugs. Shay (21) reported that 13 out of 18 depressed Vietnam veterans with PTSD exhibited improved mood and reduced aggressiveness after receiving fluoxetine. Finally, Davidson et al. (22) reported successful fluoxetine treatment of five nonveteran men and women with PTSD who had been exposed to sexual assault or industrial/motor vehicle trauma.

The only published RCT with SSRIs was carried out by van der Kolk et al. (4), who conducted a fluoxetine versus placebo RCT with 64 patients, 31 military veterans and 33 nonveteran adult survivors of childhood sexual abuse, with PTSD. Fluoxetine, but not placebo, significantly reduced overall PTSD symptomatology, especially with respect to numbing and arousal symptoms. Among the numbing/avoidant cluster of symptoms, fluoxetine was markedly effective in reducing numbing but not avoidance symptoms. It is also noteworthy that improvement in PTSD symptoms was not associated with reductions in depressive symptomatology, suggesting that

fluoxetine had a selective anti-PTSD but not antidepressant effect in this study. Civilian childhood abuse survivors were much more responsive to medication than veterans with war-related PTSD.

Other publications on SSRIs include an open trial of fluvoxamine in 24 World War II Dutch resistance fighters with PTSD (23) and the aforementioned single case report by March (20). Results in the Dutch study were more modest and less successful than in American trials with fluoxetine. De Boer et al. (23) suggest that poorer results in their study may be due to older age and longer chronicity of PTSD among the Dutch subjects, rather than to a difference in efficacy between fluoxetine and fluvoxamine.

There is one report of an open trial of clomipramine on seven Vietnam veterans with PTSD in which OCD symptoms were also monitored with the obsession subscale of the Yale-Brown OCD Scale (24). Marked reduction in PTSD intrusive symptoms was accompanied by marked reduction in the Yale-Brown obsession score in six of the seven patients, prompting the author to speculate on the relationship between PTSD intrusive and OCD obsessional thoughts.

Several important findings worth noting differentiate clinical experience with SSRI-type drugs from other agents used in PTSD.

1. SSRIs effectively reduce avoidant/numbing symptoms as well as intrusive and arousal symptoms. For the most part, other drugs have not affected these symptoms.
2. Successful treatment usually requires 10–12 weeks of drug therapy with high doses (80 mg fluoxetine, 300 mg fluvoxamine).
3. Successful treatment is often associated with gradual and incomplete reduction of symptoms rather than complete remission. (This is often the case in OCD as well.)
4. When treatment is successful, debilitating symptoms associated with PTSD often show improvement, along with core PTSD symptoms. Such associated symptoms and syndromes include rage, impulsivity, suicidal intent, depression, OCD, and behaviors associated with alcoholism or substance abuse.
5. Reduction of PTSD symptoms was not strongly associated with significant improvement in occupational function.

Buspirone

Buspirone is an anxiolytic that acts as a 5-HT_{1A} partial agonist. Only one report appears in the literature describing the response of three combat veterans (WWII, Korea, and Vietnam) to 35–60 mg buspirone (25). All three experienced marked reduction in anxiety, insomnia, flashbacks, and depressed mood. In contrast to SSRIs, however, no patient exhibited improvement in avoidant/numbing symptoms.

Cyproheptadine

Cyproheptadine is a 5-HT antagonist that has been used specifically for PTSD-related traumatic nightmares. In case reports concerning two (26) and four (27) PTSD patients, 4–28 mg cyproheptadine at bedtime successfully suppressed recurrent traumatic nightmares. Brophy (27) has now extended his initial studies to include 80 patients whose traumatic nightmares have been suppressed by cyproheptadine (Brophy, personal communication, 1992). Furthermore, administration of methysergide, a 5-HT antagonist with action similar to cyproheptadine, has reportedly reduced nightmares and improved sleep among Vietnam veterans with PTSD (Morgan, personal communication, 1992).

Drugs Affecting Both Adrenergic and Serotonergic Systems—TCAs and MAOIs

Five of six RCTs in the PTSD literature involve TCAs and/or MAOIs. Given the high comorbidity of PTSD and major depressive disorder (MDD), and the fact that these antidepressants are also effective anxiolytic and antipanic agents (28–30), it is not surprising that they have received the lion's share of attention with regard to treatment of PTSD. Open trials and case reports on the efficacy of these drugs in PTSD are reviewed elsewhere (31,32). First, we turn our attention to the five RCTs that have been published.

Although there are three RCTs with TCAs, there are enough differences between each study to make comparisons difficult. First of all, a different drug was used in each study: imipramine (33), amitriptyline (34), and desipramine (35). Second, patients with MDD were excluded from the imipramine study but not the others. Third, the imipramine and amitriptyline studies lasted 8 weeks, whereas the desipramine study lasted only 4 weeks. These differences may explain why results from these three studies differ from one another.

Frank et al. (33) conducted an 8-week RCT comparison of imipramine versus phenelzine (a MAOI) versus placebo in 34 male Vietnam veterans with combat-related PTSD. Impressive reductions in intrusive but not avoidant symptoms were seen in the imipramine (and phenelzine) group(s) in contrast to placebo controls. This study was later extended to include a total of 60 patients (19 on phenelzine, 23 on imipramine, and 18 on placebo) by Kosten et al. (36). Results were the same as those previously reported by Frank et al. Davidson et al. (34) conducted an 8-week trial of amitriptyline versus placebo in 46 male Vietnam veterans with combat-related PTSD. In contrast to Frank et al., these investigators observed only modest improvement in PTSD symptoms. Furthermore, since patients with MDD were included in the Davidson et al. (but not the Frank et al.) study, it was found that depressed PTSD patients showed greater improvement than nondepressed patients. This raised the possibility that any amelioration of PTSD symptoms was secondary to amitriptyline's antidepressant and anxiolytic potency rather than due to a specific action on core PTSD symptoms. Davidson et al. also observed a small reduction in avoidant symptoms. This is a unique finding in the TCA literature on PTSD treatment, and may be due to the fact that amitriptyline has much greater serotonergic (SSRI-type) efficacy than most other TCAs. The final RCT was a 4-week trial of desipramine versus placebo in 18 male Vietnam veterans with combat-related PTSD (35). No differences were observed between the TCA and placebo groups in this study.

The two RCTs with MAOIs also have methodological differences and contrary results, although phenelzine was used in both studies. Frank et al. (33) and Kosten et al. (36), in the study cited previously, compared phenelzine with imipramine and placebo. Again, there were marked reductions in intrusive recollections, nightmares, and flashbacks in the phenelzine (and imipramine) group(s) in comparison to the placebo group. It should be noted that phenelzine was superior to imipramine in this study. In contrast, Shestatzky et al. (37) conducted a 4-week double-blind crossover comparison between phenelzine and placebo in 10 Israeli military veterans. There was no difference between the two groups, although it should be noted that (in contrast to most studies) the placebo group showed considerable reduction in PTSD symptoms in this study.

A final word about these RCTs of TCAs and MAOIs concerns instrumentation. In all studies, PTSD symptoms were measured by the Impact of Events Scale (IES) (38). Although this scale has been very useful in PTSD research, it is limited to measurement of intrusive and avoidant symptoms, and does not monitor arousal symptoms. We might have possibly learned more about the efficacy of TCAs and MAOIs had arousal symptoms also been measured during these RCTs.

Quantitative Analysis of Open Trials, Case Reports, and RCTs with TCAs and MAOIs

While antidepressants appear to be useful for treatment of PTSD, it is unclear from the RCTs just discussed exactly which aspects of the disorder are most responsive. For example, it could be argued that antidepressants have little or no effect on PTSD specific symptoms per se, but instead produce their overall global effects by reducing comorbid symptoms of depression and anxiety/panic. Further, even if antidepressants do reduce PTSD specific symptoms clinically, it is important to know whether they affect all three symptom clusters equally.

In order to determine the specific effects of antidepressants on PTSD symptomatology, Southwick et al. (5) performed a quantitative analysis on all available published reports using antidepressants to treat PTSD. Because most reports

were not RCTs, a standard metaanalytic approach could not be used. In the quantitative analysis that was done, subjects from all 15 published reports were pooled and evaluated using a single rating scale to assess the effects on each of the three PTSD symptom clusters (reexperiencing, avoidance, hyperarousal) and on symptoms of depression and anxiety/panic. In essence, this approach allowed all subjects from the literature to be evaluated as a single sample using identical criteria for symptom improvement.

The results indicated that MAOIs were somewhat more effective than TCAs. Global response was judged to be moderate to good in 82% of subjects treated with MAOIs and in 45% of subjects taking TCAs. The response of individual symptom clusters was less pronounced, with improvement seen only in the reexperiencing cluster. Approximately 75% of subjects showed moderate or better improvement in intrusive traumatic memories, flashbacks, and nightmares, with phenelzine being superior to TCAs. Symptoms of avoidance and hyperarousal were largely unresponsive to antidepressants; the one exception was the individual symptom of insomnia that responded well to both classes of antidepressant. The quantitative analysis also suggested that a minimum of 8 weeks of treatment was needed for global improvement to occur in core PTSD symptoms.

Symptoms of depression and anxiety/panic also responded poorly to the antidepressants. For example, only 13% of phenelzine-treated and 38% of TCA-treated subjects showed a moderate or better improvement in depression. This finding is surprising given the well-known efficacy of antidepressants in treating major depression and panic disorder in non-PTSD populations. It is consistent, however, with the work of Yehuda and associates (39) suggesting that the MDD usually associated with PTSD is a very different neurobiological abnormality than endogenous depression or true melancholia (see Chapters 19 and 24).

Taken as a whole, the TCA and MAOI literature is disappointing in that so few RCTs have been carried out, no drug (except for phenelzine, which was tested twice) has been tested more than once, and, except for the recent fluoxetine study (4), no new RCTs have been published since 1991. Those early studies have helped to identify key methodological issues that must be addressed in future RCTS. Three recommendations for future research design have been proposed by Kudler et al. (40). First, any drug trial in PTSD should be carried out for a minimum of 8–10 weeks. (This recommendation is supported by quantitative analysis results indicating better outcomes in clinical trials of 8 weeks or more.) Second, observer rating instruments that are more responsive than the IES to weekly changes in symptoms should be used. And third, future research designs should include adequate controls for Axis 1 disorders that are frequently comorbid with PTSD, such as depression, alcoholism/substance abuse, and other anxiety disorders (41).

Drugs Affecting the GABA-Benzodiazepine System—Alprazolam, Clonazepam

Benzodiazepine receptors are allosterically and functionally linked to a macromolecular complex that also contains receptors for the inhibitory neurotransmitter GABA. This complex seems clearly involved in the neurobiology of stress and anxiety (42). Animal studies show that exposure to inescapable stress results in reduced benzodiazepine receptor binding (43–45). Furthermore, animals administered benzodiazepines prior to exposure to inescapable stress appear to have been protected from many adverse sequelae of this experience. The role of the GABA-benzodiazepine system may be related to alterations in other neurobiologic systems, since benzodiazepines: 1) reduce locus coeruleus activity and stress-induced increases in norepinephrine turnover 2) decrease stress-induced increases in prefrontal dopamine activity; and 3) may have their efficacy altered by endogenous steroids (46–48).

The benzodiazepine system is important to consider in PTSD because of its key involvement in human anxiety and fear states. The benzodiazepine inverse agonist, FG-7142, can produce severe anxiety and panic in healthy subjects (49),

while flumazenil, a benzodiazepine receptor antagonist, can produce panic attacks in patients with panic disorders, but not in healthy subjects (50,51). There have been no published studies on the GABA-benzodiazepine system in PTSD. A final theoretical consideration for considering benzodiazepines is the kindling model of PTSD (see next paragraph), since it has been shown that limbic kindling is associated with increased benzodiazepine receptor binding (52–54).

Likewise, there are very few clinical studies with benzodiazepines in PTSD patients, although in some settings up to 71% of PTSD patients have received benzodiazepines (55). In other settings, few PTSD patients receive benzodiazepines, because clinicians are often reluctant to prescribe these drugs given the high rates of alcoholism and chemical dependency among PTSD patients. We (56) have challenged this prescribing bias against benzodiazepines, arguing that a primary objective in treatment should be symptom reduction in patients dually diagnosed with PTSD and alcoholism/substance abuse. Citing evidence that benzodiazepines may be used safely with alcoholics when they are prescribed rationally (57), we (56) have suggested that benzodiazepines may have a valuable role in the treatment of PTSD, especially in patients who also suffer from alcoholism/substance abuse.

A final clinical concern is the rebound anxiety and severe withdrawal symptoms sometimes seen in patients taking alprazolam and other triazolo-benzodiazepine derivatives. Indeed, Risse et al. (58) reported on the severe exacerbation of PTSD symptoms among eight Vietnam veterans during withdrawal from alprazolam. These patients experienced anxiety, insomnia, rage reactions, hyperalertness, increased nightmares, intrusive thoughts, and homicidal ideation.

There are three published reports on benzodiazepine treatment of PTSD, two with alprazolam and one with clonazepam. In Feldman's (59) open trial with alprazolam, 16 of 20 veterans showed reduced insomnia, anxiety, irritability, and hyperarousal. A cautionary note from this report is the observation that four patients exhibited benzodiazepine-induced disinhibition marked by increased outbursts of anger. The only published RCT on PTSD patients treated with a benzodiazepine was a 5-week crossover trial of alprazolam versus placebo in 10 Israeli patients (3). Results indicated that alprazolam treatment was no better than placebo in reducing core PTSD symptoms, although it did produce a modest reduction in general anxiety symptoms. Finally, Lowenstein et al. (60) reported on a successful trial of clonazepam in patients whose PTSD was associated with multiple personality disorder. These patients experienced marked and sustained improvement in sleep, nightmares, flashbacks, panic attacks, and other PTSD symptoms, but exhibited no improvement in avoidance or dissociative symptoms.

We believe that benzodiazepines may have a useful role in the rational treatment of carefully selected PTSD patients. We would further recommend that future trials focus on clonazepam because of its efficacy, its low abuse potential, its safety with regard to rebound anxiety/withdrawal, and possibly because of its antikindling properties.

Antikindling Agents—Carbamazepine and Valproate

PTSD can persist for decades or even a lifetime (61,62). Therefore, a theoretical model for PTSD must include a neurobiological mechanism that precipitates and sustains long-term alteration of brain function. Kindling and behavioral sensitization are such mechanisms (see Chapter 12). They are two different neurobiological processes by which limbic and other neuroanatomic structures become increasingly sensitized following exposure to electrical stimulation or stimulant (cocaine-like) drugs. Once established, kindling and behavioral sensitization remain as stable neurobiological alterations that are associated with neurophysiological abnormalities, grand mal seizures, and aberrant behavior. Kindling was first invoked as an animal model for a psychiatric syndrome by Post and Kopanda (63), who suggested that it might account for the recurrence of episodes seen in lithium-refractory bipolar affective disorder. Kindling was proposed as a possible mechanism in PTSD (64–66)

because the chronic CNS sympathetic arousal associated with PTSD produced conditions that, it was hypothesized, might optimize neuronal sensitization of limbic nuclei.

A total of eight publications report beneficial effects from two anticonvulsants that were chosen specifically for their properties as antikindling agents. Five reports concern carbamazepine and three concern valproate. All were open trials or case reports.

Lipper et al. (64) administered carbamazepine to 10 Vietnam veterans with PTSD in an open trial. Their decision to test this drug was based on theoretical questions regarding kindling as a mechanism for PTSD. Seven patients reported marked reductions in both intensity and frequency of traumatic nightmares, flashbacks, intrusive recollections, and sleep disturbance. Three case reports on a total of five patients (67–69) describe a positive response to carbamazepine in traumatized patients who met diagnostic criteria for PTSD but who exhibited an EEG and clinical pattern consistent with complex partial seizures. Flashbacks, traumatic nightmares, and insomnia all diminished after anticonvulsant treatment. The authors emphasize the importance of ruling out complex partial seizures in any diagnostic workup of PTSD. It is for this reason, in particular, that Wolf et al.'s (70) open trial of carbamazepine in 10 Vietnam veterans with PTSD is so interesting. All of these patients had normal EEGs and no additional evidence for complex partial seizures before onset of carbamazepine treatment. Eight of the 10 patients showed improvement in impulsivity, irritability, and violent behavior, but there was no monitoring of PTSD symptoms during this trial.

Fesler (71) conducted an open trial of valproate in 16 Vietnam veterans with PTSD. She was motivated to conduct this trial because her patients could not tolerate carbamazepine and were therefore noncompliant. After administration of valproate, 10 of the 16 patients experienced marked improvement. It is noteworthy that improvement was greatest for hyperarousal and avoidant symptoms, and not for intrusion symptoms, which has been the case in other reports with antikindling agents. Finally, there are two case reports; Brodsky et al. (72) described one patient whose flashbacks were controlled by valproate, and Szymanski and Olympia (73) reported on two Vietnam veterans with PTSD who became less irritable and aggressive after valproate treatment.

Lithium

Lithium has a complex spectrum of actions on neuronal membranes, a number of neurotransmitter systems, phosphoinositide second messengers, and thyroid function. Its efficacy as a treatment for recurrent affective disorders is well established. Only two open trials of lithium have been reported. Van der Kolk (74) observed that 14 of 22 PTSD patients experienced marked reduction in autonomic arousal, a greater capacity to cope with stress, and reduced alcohol consumption following lithium treatment. It is noteworthy that none of these patients reportedly suffered from bipolar affective disorder. In a report of five cases of PTSD, Kitchner and Greenstein (75) described improvement following lithium treatment in irritability, inappropriate anger, anxiety, and insomnia. There have been no further publications on the efficacy of lithium in PTSD.

Drugs Affecting the Dopamine System—Neuroleptics

Mesocortical and frontal neurons exhibit increased dopaminergic activity following exposure to stress. There is additional evidence that chronic stress and repeated cocaine exposure may affect central dopaminergic functions (76); however, such responses may also be mediated by NMDA, opioid, substance P, or other neurotransmitter systems (77). Both animal research and clinical studies show that cocaine and amphetamines, which activate dopaminergic mechanisms, can produce hypervigilant and paranoid behavior. It is tempting to generalize from these findings to the hypervigilance, irritability, insomnia, and occasional psychotic behavior seen in PTSD patients. Such generalizations would be premature, however, because there has been little research on altered dopaminergic function

in traumatized or PTSD patients. Two studies have shown altered dopaminergic activity in traumatized patients. Jensen et al. (78) reported alterations in the growth hormone response to levodopa (L-DOPA) in sexually abused boys, and Ende et al. (79) detected elevated urinary conjugated dopamine levels among rape victims within 24 hours of the assault. Yehuda et al. (80) have detected elevated 24-hour urinary homovanillic acid levels (HVA, the major metabolite of dopamine) in Holocaust survivors and Vietnam veterans with PTSD. Hamner et al. (81) have shown an abnormal dopamine response among PTSD patients performing a treadmill task. Clearly, the role of dopamine in the pathophysiology of PTSD needs further investigation.

Research notwithstanding, neuroleptics were widely used for treating what is now recognized as PTSD during the 1970s and into the following decade. Lacking the conceptual model provided in 1980 by DSM-III (82), and impressed by the intensity of agitation, paranoid thoughts, impulsivity, explosive behavior, potential for violence, and brief psychotic or dissociative states seen in Vietnam veterans, Department of Veterans Affairs (VA) psychiatrists prescribed large quantities of neuroleptics to achieve relief of these troubling and sometimes dangerous symptoms. As clues to the pathophysiology of PTSD began to emerge, the research focus shifted to the adrenergic, HPA, and other neurobiological systems, while the pharmacological focus shifted to TCAs MAOIs, and more recently to SSRIs. As a result, there have been no RCTs, and only a single published report regarding thioridazine, on the efficacy of neuroleptics in PTSD. Dillard et al. (76) successfully treated a Vietnam veteran who was having frequent flashbacks, nightmares, anxiety, irritability, and fear of loss of control with 200 mg thioridazine. It should be pointed out, however, that this patient probably had not received an adequate trial of a TCA, MAOI, SSRI, or any other drug before thioridazine was prescribed. Despite the paucity of empirical data, a number of writers have identified special circumstances under which neuroleptics might be used (66,84–88). These include patients with refractory PTSD who exhibit paranoid behavior, overwhelming anger, aggressivity, psychotic symptoms, fragmented ego boundaries, self-destructive behavior, and frequent flashback experiences marked by auditory or visual hallucinations of traumatic episodes. It is noteworthy, however, that Mueser and Butler (85) described a group of PTSD patients with auditory hallucinations who were refractory to neuroleptic treatment.

Drugs Affecting the Opioid System—Narcotic Antagonists

There is evidence that both laboratory stress and PTSD are associated with dysregulation of the endogenous opioid system (see Chapters 6 and 18). In 1985, van der Kolk and associates (87) proposed that chronic PTSD is associated with chronic opioid depletion. Consistent with this prediction are findings that PTSD patients exhibit: 1) lower pain thresholds (32); 2) lower plasma beta endorphin levels (88); and 3) decreased production and release of methionine-enkephalin (89). Rather than opioid depletion, however, there is evidence that, upon exposure to trauma-related stimuli, PTSD patients exhibit excessive opioid activity. Pitman et al. (90) noted a nalaxone-reversible stress-induced analgesia when they exposed Vietnam veterans with PTSD to combat scenes depicted in the movie *Platoon.*

The two pharmacological studies relevant to the opioid system have emphasized excessive rather than diminished opioid function. Glover, having hypothesized that emotional numbing in PTSD results from hypersecretion of endogenous opioids (91), predicted that emotional numbing would improve following treatment with a narcotic antagonist. He administered nalmefene, a non–FDA-approved pure opiate antagonist in an open trial to 18 Vietnam veterans with PTSD (92). Nalmefene is a potent, long-acting drug that is structurally similar to both naloxone and naltrexone but has greater binding affinity to central opiate receptors. Glover reported that nalmefene (100–200 mg b.i.d.) produced marked improvement in numbing and in other PTSD symptoms in 8 of the 18 patients. The other 10 patients showed either no improve-

ment or a worsening of their PTSD, especially with regard to anxiety and panic symptoms. There is one additional publication, a single case report on successful treatment of PTSD flashbacks in two patients, with the narcotic antagonist, naltrexone (93). The article does not state whether other PTSD symptoms also responded to treatment.

Given laboratory results suggesting reduced opioid activity under some circumstances with PTSD patients, and excessive activity under other conditions, Glover's results showing a bidirectional action for a narcotic antagonist are intriguing. Future studies will need a better experimental design, better instrumentation, and a conceptual model that can account for the finding that some patients may benefit while others may worsen following from treatment with an opioid antagonist.

EVALUATION OF RESEARCH DATA

It is clear that our growing understanding of the pathophysiology of PTSD is much greater than our knowledge regarding effective pharmacological strategies for combating this complex disorder. Actually, there has been very little research on drug treatment. Even the few RCTs that have been published present interpretive difficulties for the following reasons.

1. Except for phenelzine (which was tested twice), no drug has been tested more than once.
2. Questions regarding dose and duration of treatment have not been adequately investigated.
3. Comorbid disorders frequently associated with PTSD (such as depression and substance abuse) need to be controlled for in future studies.
4. Most studies have relied too heavily on the Impact of Events Scale, an instrument that does not assess arousal symptoms. More comprehensive observer rating instruments have been developed in recent years that should be used in future studies (such as the Clinician Administered PTSD Scale (CAPS) and (SI-PTSD)).
5. Most studies have been conducted on American Vietnam veterans. Future studies need to explore patients whose PTSD was caused by something besides the trauma of war, such as rape, torture, natural disasters, or accidents. Future studies will also need to test women and PTSD patients from a variety of ethnocultural backgrounds.
6. American Vietnam veterans who have served as subjects in most published RCTs may be the most severely impaired, chronic, and treatment-refractory patient cohorts. The reason why they remain the most available patients for these drug trials is because they are still enrolled in VA treatment programs. It is possible, however, that patients who have remained in treatment after years of VA PTSD programs constitute a self-selected cohort of chronic patients with multiple levels of impairment who may be most refractory to drug (or any other) treatment. Future studies must include drug trials on different patient cohorts to make sure that lack of success of a specific drug is genuinely due to lack of pharmacological efficacy rather than due to a sampling strategy that inadvertently selects patients with the worst prognosis.
7. In studies in which symptom reduction is achieved, it is necessary to distinguish between statistical significance and clinical improvement. Too many studies have focused excessively on symptoms and paid scant attention to functional (marital, social, and vocational) status.

It is disturbing that valuable leads have not been pursued. For example, Kolb et al. (9) published their original report on clonidine and propranolol in 1984. Despite a promising study in 1988 (2) with propanolol, there have been no further investigations with that drug. Similarly, there has been no apparent attempt to replicate the exciting findings of Frank et al. (33) with phenelzine and imipramine. It appears, at present, that some momentum is gathering that will lead to extensive testing of SSRIs. While this is indeed exciting, such clinical trials should not lose sight of the multisystem pathology mani-

fested in PTSD. If, for example, SSRIs prove to be efficacious, we must not forget that there are other neurobiological systems in addition to the serotonergic system that are altered in PTSD patients.

COMPLEXITY OF PTSD

As is clear from the aforementioned literature review, there is no one medication of choice for treatment of PTSD. That is, no single medication treats the entire disorder. Instead, specific symptom clusters respond best to specific medications.

The reexperiencing symptoms respond well to both MAO inhibitors and TCAs. Reports suggest that nightmares, intrusive memories, and even flashbacks are sensitive to these medications. This finding appears relatively reliable in that it has been replicated by a number of case reports, open trials, and RCTs. Other less well-studied medications also reportedly help in reducing reexperiencing symptoms. These include clonidine, propranolol, serotonin reuptake inhibitors, and carbamazepine. However, without RCTs these findings must be considered tentative.

Hyperarousal symptoms also appear to differentially respond to various medications. The most consistent and pronounced responses have been described in case reports and open trials with the antiadrenergic agents propranolol and clonidine. Other potentially useful agents include the benzodiazepines (with the cautionary note that some patients can become emotionally disinhibited) and serotonin reuptake inhibitors. Insomnia may be especially responsive to the benzodiazepines, cyproheptadine, and trazodone. Finally, although neuroleptics may be effective in treating symptoms of agitation and hyperarousal, such use is unproven and highly controversial.

Symptoms of avoidance and numbing may be the most resistant to pharmacologic intervention. The MAOIs, TCAs, clonidine, propranolol, the benzodiazepines, lithium, and carbamazepine all appear to be ineffective in treating these symptoms. It is important to note that failure to find treatment effects may be related to the relatively brief treatment trials characteristic of PTSD research to date. It may be that avoidant/numbing symptoms improve more slowly than other PTSD symptoms, making them appear unresponsive if treatment trials are too short. The most promising agents have been the serotonin reuptake inhibitors, and one RCT showed marked reduction of psychic numbing following fluoxetine treatment (4). Valproate also merits further testing in this regard, since it produces a significant decrease in avoidant/numbing symptoms.

The frequent co-occurrence of other psychiatric disorders adds to the difficulty and challenge of rationally medicating patients with PTSD. Common comorbid Axis I disorders include major depression, panic disorder, and substance abuse disorders (41). Further, high rates of Axis II disorders (borderline, antisocial, paranoid, compulsive, and schizoid personality disorders) also have been reported among treatment-seeking combat veterans with PTSD (94). It is not yet clear whether and how well these disorders respond to pharmacologic intervention. For example, in PTSD patients, preliminary evidence suggests that comorbid panic disorder and major depression may not respond well to TCAs and MAOIs.

Although no medication studied thus far has proven effective in treating the entire disorder of PTSD, even the reduction of a single symptom may be of significant help to the individual who has been severely traumatized. For example, frequent nightmares are highly disruptive for most people. They often contribute to severe sleep deprivation, irritability, and emotionally liability. Concentration decreases, interpersonal relationships deteriorate, and job performance suffers. Clearly, a reduction of this symptom alone can have a significant effect on global functioning.

PHARMACOTHERAPY AND PSYCHOTHERAPY

The addition of a psychopharmacologic agent in the context of ongoing psychotherapy with PTSD patients can be challenging. First and foremost, such patients often find it difficult to trust other people as a consequence of their severe

traumatization. The world is often viewed as unsafe, unpredictable, and uncontrollable. Therefore, the stability of the therapeutic relationship is critical.

The therapist who works with traumatized patients must first provide a consistent, predictable, and safe environment. If pharmacotherapy is indicated, the specific meaning of medication to the patient must be carefully assessed and thoroughly understood. Will the patient view medication as a tool for increasing inner stability or as a threatening form of external control? Will the prescribing of medication be interpreted as a rejection, suggesting that the therapist prefers not to talk with the patient? Will the offer of medication suggest that the therapist no longer believes that the patient has the inner resources to combat PTSD symptoms and therefore must rely on external supports such as drugs? Finally, will the prescribing of medication foster regression and dependency?

It is also important for the therapist to understand what the decision to prescribe medication means to him or her, the therapist. Is medication being prescribed for specific symptoms that are known to be responsive to this particular agent, or is the medication being prescribed for other less overt or unconscious reasons? For example, is medication being prescribed in order to "do something" when therapy is progressing slowly? Is the prescribing of medication a way to divert attention away from aggressive and violent material that is upsetting to the therapist, so that treatment can focus on medication target symptoms such as appetite and sleep? Is the therapist unconsciously attempting to gain "control" over a difficult patient who constantly challenges authority figures such as him or herself? In other words, careful monitoring of countertransference and other therapy-related issues is absolutely essential when prescribing medication to traumatized individuals.

The staging of pharmacotherapy is also important. As noted earlier, some medications are effective in treating involuntary reexperiencing symptoms such as traumatic nightmares that occur spontaneously or in response to unavoidable trauma-related stimuli or situations. For some patients, the retrieval and processing of memories during therapy can cause a temporary but marked increase in distress from intense and uncontrollable intrusive or arousal symptoms. Indeed, therapy itself may come to be regarded as aversive if the focus on traumatic material becomes unbearable. If the patient is overwhelmed by such symptoms, he or she may drop out of therapy. It is under such conditions that the timely addition of a medication that suppresses intolerable PTSD symptoms may allow the patient to more freely experience, work through, and master the trauma, a process that many believe is essential to successful therapy. Many of the issues just discussed have been addressed in greater detail by Southwick and Yehuda (95).

The example cited in the previous paragraph applies to a therapeutic contract in which the goal of treatment is to process and master traumatic material, with the hope of reducing PTSD symptomatology. In this regard, pharmacotherapy is applied as an adjunct to psychotherapy, with the hope that drug-induced symptom reduction will permit greater depth and latitude for therapeutic exploration. In some cases, however, symptom reduction, in and of itself, may become an appropriate goal of treatment when the severity of PTSD symptoms has produced marked functional impairment or when the patient does not have the capacity to benefit from intensive psychotherapy. Under such conditions, the choice of medication will depend on which target symptoms are considered most debilitating at that time.

CONCLUSION

As attested by many chapters in this book, PTSD appears to have a unique pathophysiology that distinguishes it from other affective and anxiety disorders. Data suggest that this disorder is associated with abnormalities in a number of psychophysiologic, neurotransmitter, neuroendocrine, and psychoimmunologic systems. We do not know whether neural input from these various systems is funneled through some final common pathway that may be modified by pharmacological interventions. With our growing appreciation of the complexity of PTSD, however,

we are beginning to understand why we may have failed to discover a pharmacological silver bullet, a single drug that will significantly reduce PTSD symptoms.

There have been too few published randomized clinical trials, and no drug has been tested more than once except for phenelzine, which has been tested only twice. Even among these few published RCTs, there are enough questions about methodology, instrumentation, and sample selection to suggest the need for expansion and extension of RCT programs to include testing and retesting of more drugs. Furthermore, since most RCTs have been conducted on chronic, and possibly treatment refractory, Vietnam veterans with PTSD, it is necessary to conduct RCTs with less severely affected patients and with patients whose PTSD has been precipitated by non–war-related traumas such as sexual assault, natural disasters, and industrial accidents.

Despite these concerns, it does appear that certain drugs may be helpful in alleviating specific PTSD symptom clusters. Reexperiencing symptoms appear to respond to TCAs and MAOIs, avoidant/numbing symptoms may respond to SSRIs (and possibly to valproate), and arousal symptoms seem to respond to antiadrenergic agents. At the present time, instead of a silver bullet, there appears to be a number of drugs that may be useful in providing specific relief for selected clusters of PTSD symptoms. Therefore, a rational approach to pharmacotherapy for PTSD may require a multisystem approach in which multiple drugs, each one with a unique and distinct action, are administered simultaneously.

At the very least, pharmacotherapy has an important role as an adjunct to psychotherapy. Reduction of disruptive PTSD symptoms makes it possible for patients to participate more productively in a variety of psychotherapeutic approaches. Symptom reduction, in and of itself, is often a legitimate and highly desirable goal of treatment. Although pharmacotherapy has already begun to prove itself as a useful clinical option, research on the potential efficacy of drug treatment for PTSD is still in its infancy.

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